Answer 1:

Bibliographic Information

Rapamycin delays growth of Wnt-1 tumors in spite of suppression of host immunity. Svirshchevskaya, Elena V.; Mariotti, Jacoppo; Wright, Mollie H.; Viskova, Natalia Y.; Telford, William; Fowler, Daniel H.; Varticovski, Lyuba. Shemyakin-Ovchinnikov Institute of Bioorganic Chemistry, RAS, Moscow, Russia. BMC Cancer (2008), 8 No pp. given. Publisher: BioMed Central Ltd., CODEN: BCMACL ISSN: 1471-2407. http://www.biomedcentral.com/content/pdf/1471-2407-8-176.pdf Journal; Online Computer File written in English. CAN 149:167415 AN 2008:882397 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Rapamycin, an inhibitor of mammalian target of Rapamycin (mTOR), is an immunosuppressive agent that has anti-proliferative effects on some tumors. However, the role of Rapamycin-induced immune suppression on tumor progression has not been examd. Methods: We developed a transplantation model for generation of mammary tumors in syngeneic recipients that can be used to address the role of the immune system on tumor progression. We examd. the effect of Rapamycin on the immune system and growth of MMTV-driven Wnt-1 mammary tumors which were transplanted into irradiated and bone marrow-reconstituted, or naive mice. Results: Rapamycin induced severe immunosuppression and significantly delayed the growth of Wnt-1 tumors. T cell depletion in spleen and thymus and redn. in T cell cytokine secretion were evident within 7 days of therapy. By day 20, splenic but not thymic T cell counts, and cytokine secretion recovered. We detd. whether adoptive T cell therapy enhances the anti-cancer effect using ex vivo generated Rapamycin-resistant T cells. However, T cell transfer during Rapamycin therapy did not improve the outcome relative to drug therapy alone. Thus, we could not confirm that suppression of T cell immunity contributes to tumor growth in this model. Consistent with suppression of the mTOR pathway, decreased 4E-BP1, p70 S6-kinase, and S6 protein phosphorylation correlated with a decrease in Wnt-1 tumor cell proliferation. Conclusions: Rapamycin has a direct anti-tumor effect on Wnt-1 breast cancer in vivo that involves inhibition of the mTOR pathway at doses that also suppress host immune responses.

Answer 2:

Bibliographic Information

Anti-apoptotic and growth-stimulatory functions of CK1 delta and epsilon in ductal adenocarcinoma of the pancreas are inhibited by IC261 in vitro and in vivo. Brockschmidt, C.; Hirner, H.; Huber, N.; Eismann, T.; Hillenbrand, A.; Giamas, G.; Radunsky, B.; Ammerpohl, O.; Bohm, B.; Henne-Bruns, D.; Kalthoff, H.; Leithaeuser, F.; Trauzold, A.; Knippschild, U. Clinic of General, Visceral- and Transplantation Surgery, University of Ulm, Germany. Gut (2008), 57(6), 799-806. Publisher: BMJ Publishing Group, CODEN: GUTTAK ISSN: 0017-5749. Journal written in English. CAN 149:119002 AN 2008:751369 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: Pancreatic ductal adenocarcinomas (PDACs) are highly resistant to treatment due to changes in various signalling pathways. CK1 isoforms play important regulatory roles in these pathways. Aims: We analyzed the expression levels of CK1 delta and epsilon (CK1δ/ε) in pancreatic tumor cells in order to validate the effects of CK1 inhibition by 3-[2,4,6-(trimethoxyphenyl)methylidenyl]-indolin-2-one (IC261) on their proliferation and sensitivity to anti-CD95 and gemcitabine. Methods: CK1δ/ε expression levels were investigated by using western blotting and immunohistochem. Cell death was analyzed by FACS anal. Gene expression was assessed by real-time PCR and western blotting. The putative anti-tumoral effects of IC261 were tested in vivo in a s.c. mouse xenotransplantation model for pancreatic cancer. Results: We found that CK1δ/ε are highly expressed in pancreatic tumor cell lines and in higher graded PDACs. Inhibition of CK1δ/ε by IC261 reduced pancreatic tumor cell growth in vitro and in vivo. Moreover, IC261 decreased the expression levels of several anti-apoptotic proteins and sensitized cells to CD95-mediated apoptosis. However, IC261 did not enhance gemcitabine-mediated cell death either in vitro or in vivo. Conclusions: Targeting CK1 isoforms by IC261 influences both pancreatic tumor cell growth and apoptosis sensitivity in vitro and the growth of induced tumors in vivo, thus providing a promising new strategy for the treatment of pancreatic tumors.

Answer 3:

Bibliographic Information

Curcumin sensitizes TRAIL-resistant xenografts: molecular mechanisms of apoptosis, metastasis and angiogenesis. Shankar, Sharmila; Ganapathy, Suthakar; Chen, Qinghe; Srivastava, Rakesh K. Department of Biochemistry, University of Texas Health Science Center at Tyler, Tyler, TX, USA. Molecular Cancer (2008), 7 No pp. given. Publisher: BioMed Central Ltd., CODEN: MCOACG ISSN: 1476-4598. http://www.molecular-cancer.com/content/pdf/1476-4598-7-16.pdf Journal; Online Computer File written in English. CAN 149:191265 AN 2008:733726 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background: We have recently shown that curcumin (a diferuloylmethane, the yellow pigment in turmeric) enhances apoptosis-inducing potential of TRAIL in prostate cancer PC-3 cells, and sensitizes TRAIL-resistant LNCaP cells in vitro through multiple mechanisms. The objectives of this study were to investigate the mol. mechanisms by which curcumin sensitized TRAIL-resistant LNCaP xenografts in vivo. Methods: Prostate cancer TRAIL-resistant LNCaP cells were implanted in Balb c nude mice to examine the effects of curcumin and/or TRAIL on tumor growth and genes related to apoptosis, metastasis and angiogenesis. Results: Curcumin inhibited growth of LNCaP xenografts in nude mice by inducing apoptosis (TUNEL staining) and inhibiting proliferation (PCNA and Ki67 staining), and sensitized these tumors to undergo apoptosis by TRAIL. In xenogrfated tumors, curcumin upregulated the expression of TRAIL-R1/DR4, TRAIL-R2/DR5, Bax, Bak, p21/WAF1, and p27/KIP1, and inhibited the activation of NFκB and its gene products such as cyclin D1, VEGF, uPA, MMP-2, MMP-9, Bcl-2 and Bcl-XL. The regulation of death receptors and members of Bcl-2 family, and inactivation of NFκB may sensitize TRAIL-resistant LNCaP xenografts. Curcumin also inhibited no. of blood vessels in tumors, and circulating endothelial growth factor receptor 2-pos. endothelial cells in mice. Conclusion: The ability of curcumin to inhibit tumor growth, metastasis and angiogenesis, and enhance the therapeutic potential of TRAIL suggests that curcumin alone or in combination with TRAIL can be used for prostate cancer prevention and/or therapy.

Answer 4:

Bibliographic Information

Effect of mono and combination therapy with FTY720 and ICAM-1 mAb for mouse-to-rat cardiac xenotransplantation. Xiong, Haibo; Huang, Zufa; Ye, Qifa; Xia, Suisheng. Institute of Transplantation, Third Xiangya Hospital, Central South University, Changsha, Hunan Province, Peop. Rep. China. Zhongnan Daxue Xuebao, Yixueban (2007), 32(1), 41-46. Publisher: Zhongnan Daxue Xuebao, Yixueban Bianjibu, CODEN: ZDXYCB ISSN: 1672-7347. Journal written in Chinese. CAN 149:174031 AN 2008:426331 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Cardiac xenotransplantation was performed in abdominal site with micro-surgical technique. Recipients with xenografts were treated with different doses of FTY720 and/ or ICAM-1 mAb. Graft survival, histopathol., infiltration of CD4 +, and CD8 + T cells and levels of serum IL-2, IFNγ, IL-4, and IgM were investigated. Survival time of xenografts was (2.75±0.43)d in the controls, and survival of grafts treated with ICAM-1 mAb did not significantly improve. Treatment with large dose FTY720 led to a survival of (4.25±0.71)d ($P<0.01$). Combination therapy with large dose FTY720 and ICAM-1 mAb achieved a significant prolongation of graft survival with (10.25±2.12)d ($P<0.01$). Levels of serum IL-2, IFNγ and rat-anti-mouse IgM decreased in the combined therapy group. Pathol. lesion and infiltration of T cells in xenografts showed mitigated in the large dose combined therapy group. There was a significant neg. correlation between the antibody level and the graft survival time ($R=-0.754$, $P<0.01$). The combined therapy of FTY720 and ICAM-1 mAb can achieve a significant effect in the prolongation of heart xenograft survival and inhibition of xenoantibodies.

Answer 5:

Bibliographic Information

Adoptively transferred human lung tumor specific cytotoxic T cells can control autologous tumor growth and shape tumor phenotype in a SCID mouse xenograft model. Oflazoglu, Ezogelin; Elliott, Mark; Takita, Hiroshi; Ferrone, Soldano; Henderson, Robert A.; Repasky, Elizabeth A. Department of Immunology Roswell Park Cancer Institute, Buffalo, NY, USA. Journal of Translational Medicine (2007), 5 No pp. given. Publisher: BioMed Central Ltd., CODEN: JTMOBV ISSN: 1479-5876. http://www.translational-medicine.com/content/pdf/1479-5876-5-29.pdf Journal; Online Computer File written in English. CAN 148:119367 AN 2007:936460 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The anti-tumor efficacy of human immune effector cells, such as cytolytic T lymphocytes (CTLs), has been difficult to study in lung cancer patients in the clin. setting. Improved exptl. models for the study of lung tumor-immune cell interactions as well as for evaluating the efficacy of adoptive transfer of immune effector cells are needed. To address questions related to the in vivo interaction of human lung tumor cells and immune effector cells, we obtained an HLA class I + lung tumor cell line from a fresh surgical specimen, and using the infiltrating immune cells, isolated and characterized tumor antigen-specific, CD8+ CTLs. We then established a SCID mouse-human tumor xenograft model with the tumor cell line and used it to study the function of the autologous CTLs provided via adoptive transfer. The tumor antigen specific CTLs isolated from the tumor were found to have an activated memory phenotype and able to kill tumor cells in an antigen specific manner in vitro. Addnl., the tumor antigen-specific CTLs were fully capable of homing to and killing autologous tumors in vivo, and expressing IFN-γ, each in an antigen-dependent manner. A single injection of these CTLs was able to provide significant but temporary control of the growth of autologous tumors in vivo without the need for IL-2. The timing of injection of CTLs played an essential role in the outcome of tumor growth control. Moreover, immunohistochem. anal. of surviving tumor cells following CTL treatment indicated that the surviving tumor cells expressed reduced MHC class I antigens on their surface. These studies confirm and extend previous studies and provide addnl. information regarding the characteristics of CTLs which can be found within a patient's tumor. Moreover, the in vivo model described here provides a unique window for observing events that may also occur in patients undergoing adoptive cellular immunotherapy as effector cells seek and destory areas of tumor growth and for testing strategies to improve clin. effectiveness.

Answer 6:

Bibliographic Information

Production of nitric oxide during graft rejection is regulated by the Th1/Th2 balance, the arginase activity, and l-arginine metabolism. Holan, Vladimir; Pindjakova, Jana; Krulova, Magdalena; Neuwirth, Ales; Fric, Jan; Zajicova, Alena. Institute of Molecular Genetics, Academy of Sciences, Prague, Czech Rep. Transplantation (2006), 81(12), 1708-1715. Publisher: Lippincott Williams & Wilkins, CODEN: TRPLAU ISSN: 0041-1337. Journal written in English. CAN 146:79310 AN 2006:607867 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Prodn. of nitric oxide (NO) by graft infiltrating macrophages has been proposed as an important effector mechanism of allograft rejection. Although high levels of NO are generated during allograft rejection, undetectable or only limited amts. of NO were found in rejected skin xenografts. BALB/c mice were grafted with skin transplants from syngeneic, allogeneic or xenogeneic (rat) donors. The prodn. of NO, cytokines and arginase in the grafts was detd. by spectrophotometry, ELISA, or polymerase chain reaction. Effects of depletion of CD4 cells, neutralization of interleukin (IL)-4 or application of arginase inhibitors N-hydroxy-L-arginine (L-NOHA) and L-valine on prodn. of NO in rejected xenografts were evaluated. Rejection of rat skin xenografts, on the contrary to rejection of allografts, was assocd. with a local high prodn. of Th2 cytokines IL-4 and IL-10, overexpression of arginase genes, strongly enhanced arginase activity and attenuated NO generation in the graft. The supernatants obtained after cultivation of skin xenograft (but not allograft or syngeneic graft) explants contained a high arginase activity and strongly suppressed NO prodn. by activated macrophages. This suppression was completely inhibited by L-NOHA or was overcome by an excess of exogenous L-arginine, a substrate for NO synthesis. Cocultivation of xenograft explants that did not produce NO with arginase inhibitors L-NOHA or L-valine restored NO generation in the graft. The results suggest that upregulation of arginase activity by Th2 cytokines during xenograft rejection limits the bioavailability of L-arginine for the inducible NO synthase and thus attenuates generation of NO by the graft-infiltrating macrophages.

Answer 7:

Bibliographic Information

Gene Therapy That Safely Targets and Kills Tumor Cells Throughout the Body. Hurtado, Alicia; Tseng, Jen-Chieh; Meruelo, Daniel. Department of Pathology, New York University School of Medicine, New York, NY, USA. Rejuvenation Research (2006), 9(1), 36-44. Publisher: Mary Ann Liebert, Inc., CODEN: RREEC2 ISSN: 1549-1684. Journal written in English. CAN 145:305848 AN 2006:332624 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The authors studied the therapeutic value of Sindbis vectors for advanced metastatic cancer by using a variety of clin. accurate mouse models and demonstrated through imaging, histol., and mol. data that Sindbis vectors systemically and specifically infect/detect and kill metastasized tumors in vivo, leading to significant suppression of tumor growth and enhanced survival. Use of two different bioluminescent genetic markers for the IVIS Imaging System (Xenogen Corp., Alameda, CA) permitted demonstration of an excellent correlation between vector delivery and metastatic locations in vivo. Sindbis tumor specificity is not attributable to a species difference between human tumor and mouse normal cells. Sindbis virus is known to infect mammalian cells using the Mr 67,000 laminin receptor, which is elevated in tumor vs. normal cells, and downregulated expression of laminin receptor with small interfering RNA significantly reduces the infectivity of Sindbis vectors. Tumor overexpression of the laminin receptor may explain the specificity and efficacy that Sindbis vectors demonstrate for tumor cells in vivo. Laser capture microdissection of mouse tumor implants showed equiv. laminin receptor expression levels in the different tumor metastases in the peritoneal cavity. Incorporation of antitumor cytokine genes such as interleukin- 12 and interleukin-15 genes enhances the efficacy of the vector. These results suggest that Sindbis viral vectors may be promising agents for both specific detection and growth suppression of metastatic ovarian cancer.

Answer 8:

Bibliographic Information

Antitumor effects of IDN5109 on head and neck squamous cell carcinoma. Sano, Daisuke; Matsuda, Hideki; Ishiguro, Yukari; Nishimura, Goshi; Kawakami, Mariko; Tsukuda, Mamoru. Department of Biology and Function in the Head and Neck, Yokohama City University Graduate School of Medicine, 3-9 Fukuura, Kanazawa-ku, Yokohama, Japan. Oncology Reports (2006), 15(2), 329-334. Publisher: Oncology Reports, CODEN: OCRPEW ISSN: 1021-335X. Journal written in English. CAN 145:95904 AN 2006:150821 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Taxanes, a new class of antitumor drugs, are effective against a large no. of human tumors, although there are problems with drug resistance. The novel taxane, IDN5109, is characterized by its high tolerability, antitumor efficacy, ability to overcome multidrug resistance, and oral bioavailability. We investigated the cellular response of IDN5109 to head and neck squamous cell carcinoma (HNSCC), and compared the antitumor activity of IDN5109 with that of paclitaxel. This is the first demonstration of antitumor effects of IDN5109 on HNSCC. In in vitro expts., IDN5109 showed antiproliferative effects against HNSCC cell lines. After treatment with IDN5109, Bcl-2 and Bcl-XL were down-regulated, Bax was up-regulated, and caspase-3 was activated. After treatment with IDN5109, concns. of both VEGF and IL-8 in the culture supernatant of HNSCC cells decreased. In in vivo expts., the oral administration of IDN5109 showed antitumor effects against HNSCC tumor xenografts. Immunohistochem. showed that IDN5109 inhibited tumor angiogenesis and induced apoptosis in HNSCC cells, producing a decreased blood vessel d. and increased apoptosis index. On the basis of these results, IDN5109 is useful as a chemotherapeutic agent against HNSCC.

Answer 9:

Bibliographic Information

Growth inhibition of human hepatocellular carcinoma xenograft in nude mice by combined treatment with human

cytokine-induced killer cells and chemotherapy. Shi, Ming; Yao, Li; Wang, Fusheng; Lei, Zhouyun; Zhang, Bing; Li, Wenliang; Liu, Jingchao; Tang, Zirong; Zhou, Guangde. Division of Biological Engineering, Beijing Institute of Infectious Disease, the 302 Hospital of PLA, Beijing, Peop. Rep. China. Zhonghua Zhongliu Zazhi (2004), 26(8), 465-468. Publisher: Zhongguo Yixue Kexueyuan, Zhongguo Xiehe Yike Daxue, Zhongliu Yanjiuso, Zhongliu Yiyuan, CODEN: CCLCDY ISSN: 0253-3766. Journal written in Chinese. CAN 144:466311 AN 2005:1280394 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The inhibitory effects of cytokine-induced killer (CIK) cells alone, chemotherapeutic drug alone, and CIK cells combined with chemotherapeutic drug on the growth of hepatocellular carcinoma (HCC) cells transplanted in nude mice were compared. Peripheral blood mononuclear cells (PBMC) collected from five healthy donors by blood cell separator were incubated in vitro to induce CIK cells in the presence of interferon-gamma(IFN-γ), IL-2 and anti-CD3 monoclonal antibody (mAb). The phenotype of CIK cells was characterized by flow cytometric anal. BEL-7402 HCC cells were inoculated s.c. to nude mice. On day 5, at the inoculation site were injected normal saline (group 1), CIK cells (3 x 107 and 6 x 107, group 2 and 3), mitomycin-C (MMC 80 μg in 0.2 mL, group 4), and CIK cells combined with MMC (group 5), resp. The percentage of CD3+, CD3+CD8+, CD3+CD56+, CD25+ cells increased from 64.0%, 28.0%, 7.8%, and 9.1% to 94.7%, 67.7%, 61.3%, and 84.0% resp. after cytokine induction. The percentage of CD3+ and CD3+CD8+ cells remained at high levels during incubation period, but that of CD25+ and CD3+CD56+ cells peaked resp. on day 7 and 13 and then declined. During the 90-day observation, the tumor formation rates were 100%, 70.0%, 80.0%, 70.0% and 66.7%; and the mouse survival rates were 10.0%, 60.0%, 40.0%, 50.0% and 75.0%, resp. from group 1 to group 5. Compared to the other groups, in the combined therapy group of mice, not only the tumor grew slowly and but also showed more marked tissue necrosis. The growth inhibitory effect on human HCC transplanted in nude mice of combined CIK cells and MMC treatment is more potent than that of CIK cells or MMC alone.

Answer 10:

Bibliographic Information

Immunomodulatory Drug CC-5013 or CC-4047 and Rituximab Enhance Antitumor Activity in a Severe Combined Immunodeficient Mouse Lymphoma Model. Hernandez-Ilizaliturri, Francisco J.; Reddy, Nishitha; Holkova, Beata; Ottman, Edris; Czuczman, Myron S. Department of Medicine, State University of New York at Buffalo, Buffalo, NY, USA. Clinical Cancer Research (2005), 11(16), 5984-5992. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 144:63981 AN 2005:864117 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

New thalidomide derivs. CC-5013 and CC-4047 (immunomodulatory drugs, IMiD) are up to 10,000 times more potent than Thalidomide. The biol. effects of IMiDs are presumed to be mediated by (a) activation of some components of the innate [natural killer (NK) cells] or adoptive immune system (T cells), (b) modification of cytokine microenvironment in the tumor bed, or by (c) inhibition of angiogenesis. In this article, we tested an innovative combination strategy involving rituximab and IMiDs in aggressive lymphoma cell lines and human lymphoma xenografts. Treatment of non-Hodgkin's lymphoma cells with CC-5013 resulted in a 40% to 70% growth inhibition when compared with controls ($P < 0.05$). Exposure of lymphoma cells to CC-4047 resulted in a lesser degree of growth inhibition. Induction of apoptosis was shown in 10% to 26% of lymphoma cells 24 h following exposure to either IMiD. In vivo studies in severe combined immunodeficient mice showed synergistic activity between CC-4047 (and to a lesser degree, CC-5013) plus rituximab. Animals treated with the CC-4047/rituximab combination had a median survival of 74 days ($P = 0.0012$) compared with 58 days ($P = 0.167$) in CC-5013/rituximab-treated animals compared with 45 days in rituximab monotherapy-treated animals. The synergistic effect between IMiDs and rituximab in our mouse model was attributed to NK cell expansion. The enhancement of rituximab activity by IMiDs was abrogated by in vivo depletion of NK cells. Augmenting NK cell function by CC-4047 or CC-5013 exposure may increase the antitumor effects of rituximab against B-cell lymphomas and warrants further exploration in the context of a clin. trial.

Answer 11:

Bibliographic Information

Human short-term repopulating stem cells are efficiently detected following intrafemoral transplantation into NOD/SCID recipients depleted of CD122+ cells. McKenzie, Joby L.; Gan, Olga I.; Doedens, Monica; Dick, John E. Department of Molecular and Medical Genetics, University of Toronto and Division of Cell and Molecular Biology, University Health Network, Toronto, ON, Can. Blood (2005), 106(4), 1259-1261. Publisher: American Society of Hematology, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. CAN 143:304559 AN 2005:843041 CAPLUS

Abstract

The nonobese diabetic/severe combined immune deficiency (NOD/SCID) xenotransplantation model has emerged as a widely used assay for human hematopoietic stem cells; however, barriers still exist that limit engraftment. We previously identified a short-term SCID-repopulating cell (SRC) following direct intrafemoral injection into NOD/SCID mice, whereas others characterized similar SRCs using NOD/SCID mice depleted of natural killer (NK) cell activity. To det. the model that most efficiently detects short-term SRCs, we compared human engraftment in 6 different xenotransplantation models: NOD/SCID-β2-microglobulin-null mice, anti-CD122 (interleukin-2 receptor β [IL-2Rβ])-treated or unmanipulated NOD/SCID mice, each given transplants by i.v. or intrafemoral injection. Human cell engraftment was highest in intrafemorally injected anti-CD122-treated NOD/SCID mice compared to all other groups at 2 and 6 wk after transplantation. These modifications to the SRC assay provide improved detection of human stem cells and demonstrate that CD122+ cells provide barriers to stem cell engraftment, a finding with potential clin. relevance.

Answer 12:

Bibliographic Information

Corneal rat-to-mouse xenotransplantation and the effects of anti-CD4 or anti-CD8 treatment on cytokine and nitric oxide production. Pindjakova, Jana; Vitova, Andrea; Krulova, Magdalena; Zajicova, Alena; Filipec, Martin; Holan, Vladimir. Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, Czech Rep. Transplant International (2005), 18(7), 854-862. Publisher: Blackwell Publishing Ltd., CODEN: TRINE5 ISSN: 0934-0874. Journal written in English. CAN 143:345193 AN 2005:798964 CAPLUS

Abstract

Corneal xenotransplantation may be an alternative approach to overcome shortage of allografts for clin. transplantation. Orthotopic corneal rat-to-mouse xenotransplantation and syngeneic transplantation were performed and the effects of anti-CD4 and anti-CD8 treatments on corneal xenograft survival and prodn. of cytokines, interleukin (IL)-2, IL-4, IL-10, γ-interferon (IFN-γ), and nitric oxide (NO) were evaluated. RT-PCR was used to det. the expression of genes for cytokines and inducible nitric oxide synthase (iNOS) in the grafts. The presence of iNOS protein in grafts was detected by immunofluorescent staining. The authors found that corneal xenotransplantation was assocd. with a strong upregulation of genes for both Th1 and Th2 cytokines and with NO prodn. in the graft. Treatment of xenograft recipients with mAb anti-CD4, but not anti-CD8, resulted in a profound inhibition of IL-2, IL-4, and IL-10 prodn., and in prolongation of corneal xenograft survival. The results show that upregulation of Th2 cytokines after corneal xenotransplantation does not correlate with xenograft rejection. Rather, corneal graft rejection is assocd. with the expression of genes for IFN-γ and iNOS and with NO prodn.

Answer 13:

Bibliographic Information

Inhibition of Cellular Immune Responses to Encapsulated Porcine Islet Xenografts by Simultaneous Blockade of Two Different Costimulatory Pathways. Safley, Susan A.; Kapp, Linda M.; Tucker-Burden, Carol; Hering, Bernhard; Kapp, Judith A.; Weber, Collin J. Department of Surgery, Emory University School of Medicine, Atlanta, GA, USA. Transplantation (2005), 79(4), 409-418. Publisher: Lippincott Williams & Wilkins, CODEN: TRPLAU ISSN: 0041-1337. Journal written in English. CAN 142:480385 AN 2005:159650 CAPLUS

Abstract

Transplantation of human islets has been successful clin. Since human islets are scarce, we are studying microencapsulated porcine islet xenografts in nonobese diabetic (NOD) mice. We have evaluated the cellular immune response in NOD mice with and without dual costimulatory blockade. Alginate-poly-L-lysine-encapsulated adult porcine islets were transplanted i.p. in untreated diabetic NODs and NODs treated with CTLA4-Ig to block CD28/B7 and with anti-CD154 mAb to inhibit CD40/CD40-ligand interactions. Groups of mice were sacrificed on subsequent days; microcapsules were evaluated by histol.; peritoneal cells were analyzed by FACS; and peritoneal cytokines were quantified by ELISA. Controls included immunoincompetent NOD-SCIDS and diabetic NODs given sham surgery or empty microcapsules. Within 20 days, encapsulated porcine islets induced accumulation of large nos. of macrophages, eosinophils, and significant nos. of CD4+ and CD8+ T cells at the graft site, and all grafts were rejected. During rejection, IFNγ, IL-12 and IL-5 were significantly elevated over sham-operated controls, whereas IL-2, TNFα, IL-4, IL-6, IL-10, IL-1β and TGFβ were unchanged. Treatment with CTLA4-Ig and anti-CD154 prevented graft destruction in all animals during the 26 days of the expt., dramatically inhibited recruitment of host inflammatory cells, and inhibited peritoneal IFNγ and IL-5 concns. while delaying IL-12 prodn. When two different pathways of T cell costimulation were blocked, T cell-dependent inflammatory responses were inhibited, and survival of encapsulated islet xenografts was significantly prolonged. These findings suggest synergy between encapsulation of donor islets and simultaneous blockade of two host costimulatory pathways in prolonging xenoislet transplant survival.

Answer 14:

Bibliographic Information

Combination therapy for adult T-cell leukemia-xenografted mice: flavopiridol and anti-CD25 monoclonal antibody. Zhang, Meili; Zhang, Zhuo; Goldman, Carolyn K.; Janik, John; Waldmann, Thomas A. Metabolism Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD, USA. Blood (2005), 105(3), 1231-1236. Publisher: American Society of Hematology, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. CAN 142:309411 AN 2005:114361 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Adult T-cell leukemia (ATL) develops in a small proportion of individuals infected with human T-cell lymphotrophic virus-1. The leukemia consists of an overabundance of activated T cells, which express CD25 on their cell surfaces. Presently, there is no accepted curative therapy for ATL. Flavopiridol, an inhibitor of cyclin-dependent kinases, has potent antiproliferative effects and antitumor activity. The authors investigated the therapeutic efficacy of flavopiridol alone and in combination with humanized anti-Tac antibody (HAT), which recognizes CD25, in a murine model of human ATL. The ATL model was established by i.p. injection of MET-1 leukemic cells into nonobese diabetic/severe combined immunodeficient mice. Either flavopiridol, given 2.5 mg/kg body wt. daily for 5 days, or HAT, given 100 μg weekly for 4 wk, inhibited tumor growth as monitored by serum levels of human β-2-microglobulin (β2.mu.; $P < .01$), and prolonged survival of the leukemia-bearing mice ($P < .05$) as compared with the control group. Combination of the 2 agents dramatically enhanced the antitumor effect, as shown by both β2.mu. levels and survival of the mice, when compared with those in the flavopiridol or HAT alone group ($P < .01$). The significantly improved therapeutic efficacy by combining flavopiridol with HAT provides support for a clin. trial in the treatment of ATL.

Answer 15:

Bibliographic Information

In vitro and in vivo antitumor activity of anti-CD3/anti-B cell carcinoma bispecific antibody. Xu, Yuanfu; Xiong, Dongsheng; Yang, Chunzheng; Shao, Xiaofeng; Peng, Hui; Fan, Dongmei; Liu, Hanzhi; Lai, Zengzu; Gao, Yingdai; Zhu, Zhenping. The State Key Laboratory of Experimental Hematology, Institute of Hematology, Chinese Academy of Medical Sciences + Peking Union Medical College, Tianjin, Peop. Rep. China. Gaojishu Tongxun (2003), 13(8), 33-38. Publisher: Gaojishu Tongxun Zazhishe, CODEN: GTONE8 ISSN: 1002-0470. Journal written in Chinese. CAN 142:85962 AN 2004:520565 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The in vitro and in vivo biol. activities of the anti-CD3/anti-B cell carcinoma (CD20+) bispecific antibody were studied. The kind of engineering antibody could bind to Jurkat cell and Daudi cell (CD20+) simultaneously, and the antibody could cross-link those two types cells to form cellular resetting, the affinity const. (Ka) of them was 3.2 x 108 M-1 and 8.9 x 108 M-1, resp. In vitro, the engineering antibody could efficiently activate human T cell to lyse B lymphoma cells in a dose-dependent manner. In vivo, 125I labeled anti-CD3/anti-CD20 antibody localized preferentially in s.c. implanted Raji tumor in nude mice. Administered along with interleukin-2 (IL-2) and T-enriched human PBMC, the antibody could recruit T cells to kill B lymphoma cell (CD20+), inhibit the growth of xenografted human B lymphoma in the nude mice, and significantly prolong the survival of tumor-bearing nude mice.

Answer 16:

Bibliographic Information

Redirected T-cell cytotoxicity to epithelial cell adhesion molecule-overexpressing adenocarcinomas by a novel recombinant antibody, E3Bi, in vitro and in an animal model. Ren-Heidenreich, Lifen; Davol, Pamela A.; Kouttab, Nicola M.; Elfenbein, Gerald J.; Lum, Lawrence G. Molecular Immunology Laboratory, Adele R. Decof Cancer Center, Roger Williams Hospital, Providence, RI, USA. Cancer (New York, NY, United States) (2004), 100(5), 1095-1103. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 140:373649 AN 2004:233224 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

BACKGROUND. To redirect cytotoxic T cells to target a broad range of adenocarcinomas, the authors constructed a novel, recombinant, bispecific antibody, E3Bi, directed at the tumor-assocd. antigen, epithelial cell adhesion mol. (EpCAM), and the CD3 receptor on T cells. METHODS. T cells were prepd. from healthy blood donors. The cytotoxicity of activated T cells (ATC) redirected to tumor cells by E3Bi was measured with in vitro 51Cr release assays. In vivo studies were performed in a severe combined immunodeficient (SCID)/Beige mouse xenograft model. Tumor-bearing mice were treated with low doses (1 mg/kg) or high doses (10 mg/kg) of E3Bi along with ATC (2.times.109 cells/kg), and treatment efficacy was evaluated both by ex vivo tumor cell survival assay after in vivo treatments and by in vivo tumor growth delay studies. RESULTS. In vitro, targeting the EpCAM-overexpressing human tumor cell lines with E3Bi increased specific cytotoxicity of ATC by >70% at an effector-to-target ratio of 2.5; this cytotoxicity was abolished competitively in the presence of an anti-EpCAM monoclonal antibody. In contrast, E3Bi did not enhance ATC cytotoxicity toward the low EpCAM-expressing tumor cell line. In ex vivo tumor cytotoxicity assays, a significant redn. in tumor cell survival (40% with low-dose E3Bi; 90% with high-dose E3Bi) was obsd. in E3Bi/ATC-treated mice compared with control mice that were treated with ATC only. In addn., SCID/Beige mice xenografted with LS174T tumors demonstrated a significant tumor growth delay after receiving E3Bi/ATC/interleukin 2 (IL-2) compared with mice that received ATC/IL-2 alone. CONCLUSIONS. E3Bi specifically and very efficiently redirected T cells to destroy EpCAM-overexpressing tumors both in vitro and in an animal model. These results suggest a therapeutic utility for E3Bi in the treatment of adenocarcinomas.

Answer 17:

Bibliographic Information

Liposome-mediated cytokine gene delivery to human tumor xenografts. Egilmez, Nejat K.; Bankert, Richard B. Department of Microbiology, SUNY at Buffalo, Buffalo, NY, USA. Methods in Enzymology (2003), 373(Liposomes, Part C), 529-535. Publisher: Elsevier, CODEN: MENZAU ISSN: 0076-6879. Journal written in English. CAN 140:326755 AN 2004:192941 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The human tumor/SCID mouse xenograft model provides a system in which gene transfer protocols can be evaluated in human tumors in vivo before clin. use. Moreover, this model represents a convenient assay for correlating cytokine gene-transfer efficacy with in vivo antitumor activity for selected human cytokines. In particular, this model has been used to optimize in vivo gene-transfer strategies involving human interleukin-2 (IL-2) expression plasmids. A further improvement of the model involves co-engraftment of

human tumors and human PBL into SCID mice, which allows the evaluation of species-specific cytokines such as IL-12.

Answer 18:

Bibliographic Information

Prolonged survival of rat islet xenografts in mice after CD45RB monotherapy. Visser, Lydia; Poppema, Sibrand; de Haan, Bart; Klok, Pieter; van der Leij, Judith; van den Berg, Anke; de Vos, Paul. Department of Pathology and Laboratory Medicine, University of Groningen, Groningen, Neth. Transplantation (2004), 77(3), 386-391. Publisher: Lippincott Williams & Wilkins, CODEN: TRPLAU ISSN: 0041-1337. Journal written in English. CAN 141:241718 AN 2004:122716 CAPLUS

Abstract

BACKGROUND: Pancreatic islet transplantation can correct the disordered glucose metab. of type 1 diabetes, but the no. of successful transplants has been low because of the need for long-term immunosuppression and the limited availability of human islets. New approaches, such as the use of tolerance-inducing treatment modalities and the use of islets of nonhuman sources, can possibly improve the success of islet transplantation. In the present study, the authors investigated the effect of anti-CD45RB treatment on the survival of islet xenografts. METHODS: Chem. induced diabetic mice underwent xenografting with rat islets and were treated with CD45RB antibodies on days -1, 0, and 5. Immunohistol. and real-time polymerase chain reaction were used to study the effect of the treatment in the xenografts. The effect of anti-CD45RB treatment in peripheral blood of normal mice was measured with flow cytometry. RESULTS: In the treated mice, survival of the grafts was prolonged substantially. In the treated mice with functioning grafts, no lymphocytes were found infiltrating the transplanted islets on day 6; whereas in the untreated animals with functioning grafts, signs of rejection were evident. In the grafts of the treated animals, significantly less mRNA for interleukin (IL)-2, interferon-γ, and IL-4 was found compared with the untreated mice. After CD45RB treatment, there was depletion or decrease of CD45RBbright cells from the peripheral blood. CONCLUSIONS: Our results show that a short course of anti-CD45RB monotherapy prolongs the survival of rat islet xenografts in C57BL/6 mice.

Answer 19:

Bibliographic Information

Development of both human connective tissue-type and mucosal-type mast cells in mice from hematopoietic stem cells with identical distribution pattern to human body. Kambe, Naotomo; Hiramatsu, Hidefumi; Shimonaka, Mika; Fujino, Hisanori; Nishikomori, Ryuta; Heike, Toshio; Ito, Mamoru; Kobayashi, Kimio; Ueyama, Yoshito; Matsuyoshi, Norihisa; Miyachi, Yoshiki; Nakahata, Tatsutoshi. Department of Pediatrics and Dermatology, Kyoto University Graduate School of Medicine, Kyoto, Japan. Blood (2004), 103(3), 860-867. Publisher: American Society of Hematology, CODEN: BLOOAW ISSN: 0006-4971. Journal written in English. AN 2004:102689 CAPLUS

Abstract

The transplantation of primitive human cells into sublethally irradiated immunedeficient mice is the well-established in vivo system for the investigation of human hematopoietic stem cell function. Although mast cells are the progeny of hematopoietic stem cells, human mast cell development in mice that underwent human hematopoietic stem cell transplantation has not been reported. Here we report on human mast cell development after xenotransplantation of human hematopoietic stem cells into nonobese diabetic severe combined immunodeficient (NOD/SCID)/γcnull (NOG) mice with severe combined immunodeficiency and interleukin 2 (IL-2) receptor γ-chain allelic mutation. Supported by the murine environment, human mast cell clusters developed in mouse dermis, but they required more time than other forms of human cell reconstitution. In lung and gastric tract, mucosal-type mast cells contg. tryptase but lacking chymase located on gastric mucosa and in alveoli, whereas connective tissue-type mast cells contg. both tryptase and chymase located on gastric submucosa and around major airways, as in the human body. Mast cell development was also obsd. in lymph nodes, spleen, and peritoneal cavity but not in the peripheral blood. Xenotransplantation of human hematopoietic stem cells into NOG mice can be expected to result in a highly effective model for the investigation of human mast cell development and function in vivo.

Answer 20:

Bibliographic Information

Progress of gene therapy for esophageal cancer in Japan. Matsubara, Hisahiro; Ochiai, Takenori. Dept. of Academic Surgery, Graduate School of Medicine, Chiba University, Japan. Gan to Kagaku Ryoho (2003), 30(7), 944-949. Publisher: Gan to Kagaku Ryohosha, CODEN: GTKRDX ISSN: 0385-0684. Journal; General Review written in Japanese. CAN 140:70020 AN 2003:643825 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Retrovirally expressed interleukin-2 gene, granulocyte macrophage-colony stimulating factor gene, herpes simplex virus-thymidine kinase gene and p53 gene in human esophageal cancer cells showed antitumor effects in a nude mice xenotransplant model. We established a clin. protocol of gene therapy for advanced esophageal cancer using the wild type p53 gene with an adenovirus vector. In Dec. of 2000, we began the first tumor suppressor gene therapy trial. Now, this trial, which has 9 patients. There have been no serious adverse event excluding fever and local pain. The feasibility of this treatment appears fairly good in these 9 cases. Furthermore, we developed a new method for transducing genes without a virus vector since a virus vector has several potentially unwanted properties. In vivo electroporation is a useful strategy for cancer gene therapy. Moreover, elec. pulse to established solid tumors increases intracellular concns. of chemotherapeutic agents. Transduction of the wild-type p53 gene by electroporation decreased the amt. of nedaplatin required for tumor suppression. Electrochemo-gene therapy is a relatively simple method and can produce a better therapeutic effect.

Answer 21:

Bibliographic Information

A mutated superantigen SEA D227A fusion diabody specific to MUC1 and CD3 in targeted cancer immunotherapy for bile duct carcinoma. Takemura, Shin-ichi; Kudo, Toshio; Asano, Ryutaro; Suzuki, Masanori; Tsumoto, Kouhei; Sakurai, Naoki; Katayose, Yu; Kodama, Hideaki; Yoshida, Hiroshi; Ebara, Shinji; Saeki, Hisaaki; Imai, Kohzoh; Matsuno, Seiki; Kumagai, Izumi. First Department of Surgery, Tohoku University School of Medicine, Sendai, Japan. Cancer Immunology Immunotherapy (2002), 51(1), 33-44. Publisher: Springer-Verlag, CODEN: CIIMDN ISSN: 0340-7004. Journal written in English. CAN 137:184119 AN 2002:344409 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In cancer immunotherapy research, many bispecific antibodies (BsAbs) have been developed for directing T cells toward tumor cells. Recent advances in genetic engineering have made it possible to prep. Ig fragments consisting of variable domains using bacterial expression systems. Therefore, recombinant BsAbs, termed diabodies, have attracted particular attention. The authors have previously produced an anti-MUC1 × anti-CD3 diabody (M×3 diabody) in an Escherichia coli (E. coli) expression system. In order to reinforce the antitumor effects of the Mx3 diabody, mutated superantigen staphylococcal enterotoxin A (SEA) D227A was genetically fused to the M×3 diabody. The SEA D227A fusion M×3 diabody (SEA D227A-M×3 diabody) thus constructed showed remarkable MUC1-specific antitumor effects when used with effector cells (lymphokine-activated killer cells with T-cell phenotype [T-LAK] and peripheral blood mononuclear cells [PBMCs]). In the bile duct carcinoma (BDC)-xenografted severe combined immunodeficient (SCID) mouse model, it also demonstrated strong antitumor activity when administered i.v. together with T-LAK cells and interleukin-2 (IL-2). In this expt., the complete disappearance of tumors was obsd. in 3 out of 6 mice, and the other 3 showed marked retardation of tumor growth. Therefore, the SEA D227A-Mx3 diabody is considered to be a promising reagent in specific targeted immunotherapy for BDC and other MUC1-pos. carcinomas. This is the first report on a diabody that is effective in treating human solid cancers in the xenografted SCID mouse exptl. model.

Answer 22:

Bibliographic Information

Cytokines delivered by biodegradable microspheres promote effective suppression of human tumors by human peripheral blood lymphocytes in the SCID-Winn model. Egilmez, Nejat K.; Jong, Yong S.; Hess, Stephen D.; Jacob, Jules S.; Mathiowitz, Edith; Bankert, Richard B. Department of Immunology, Roswell Park Cancer Institute, Buffalo, NY, USA. Journal of Immunotherapy (2000), 23(2), 190-195. Publisher: Lippincott Williams & Wilkins, CODEN: JOIMF8 ISSN: 1053-8550. Journal written in English. CAN 133:236655 AN 2000:243186 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A new technol. for the local and sustained delivery of immunostimulatory mols. to the tumor environment for cancer immunotherapy was evaluated. The ability of cytokines delivered by biodegradable microspheres to promote the antitumor activity of human peripheral blood lymphocytes (PBL) was tested in a human PBL, human tumor, and SCID mouse (SCID-Winn) model. Co-engraftment of human recombinant IL-12-loaded microspheres with human PBL and tumors in SCID mice promoted complete tumor suppression in as many as 100% of the mice, whereas microspheres loaded with polyethyleneglycol-interleukin-2 suppressed but did not eliminate the growth of tumor xenografts. Control microspheres (loaded with bovine serum albumin) in the presence of human PBL or cytokine-loaded microspheres in the absence of human PBL had no tumor-suppressive effect. Coincident with the enhancement of the human PBL-mediated antitumor activity in mice treated with IL-12-loaded microspheres was the prodn. and release of human IFN-γ indicating that IL-12 released from the microspheres results in the activation of the engrafted human PBL. The results establish that biodegradable microspheres represent an effective tool for the local and sustained delivery of cytokines to the tumor environment for cancer immunotherapy.

Answer 23:

Bibliographic Information

Responsiveness of human prostate carcinoma bone tumors to interleukin-2 therapy in a mouse xenograft tumor model. Kocheril, Sosa V.; Grignon, David J.; Wang, Ching Y.; Maughan, Richard L.; Montecillo, Emily J.; Talati, Bharat; Tekyi-Mensah, Samuel; Pontes, J. Edson; Hillman, Gilda G. Department of Urology, Barbara Ann Karmanos Cancer Institute, Wayne State University School of Medicine and Harper Hospital, Detroit, MI, USA. Cancer Detection and Prevention (1999), 23(5), 408-416. Publisher: Blackwell Science, Inc., CODEN: CDPRD4 ISSN: 0361-090X. Journal written in English. CAN 132:136230 AN 1999:647326 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We have tested an immunotherapy approach for the treatment of metastatic prostate carcinoma using a bone tumor model. Human PC-3 prostate carcinoma tumor cells were heterotransplanted into the femur cavity of athymic Balb/c nude mice. Tumor cells replaced marrow cells in the bone cavity, invaded adjacent bone and muscle tissues, and formed a palpable tumor at the hip joint. PC-3/IF cell lines, generated from bone tumors by serial in vivo passages, grew with faster kinetics in the femur and metastasized to inguinal lymph nodes. Established tumors were treated with systemic interleukin-2 (IL-2) injections. IL-2 significantly inhibited the formation of palpable tumors and prolonged mouse survival at nontoxic low doses. Histol. IL-2 caused vascular damage and infiltration of polymorphonuclear cells and lymphocytes in the tumor as well as necrotic areas with apoptotic cells. These findings suggest destruction of tumor cells by systemic IL-2 therapy and IL-2 responsiveness of prostate carcinoma bone tumors.

Answer 24:

Bibliographic Information

Cytokine immunotherapy of cancer with controlled release biodegradable microspheres in a human tumor xenograft/SCID mouse model. Egilmez, Nejat K.; Jong, Yong S.; Iwanuma, Yoshimi; Jacob, Jules S.; Santos, Camilla A.; Chen, Fang-An; Mathiowitz, Edith; Bankert, Richard B. Department of Molecular Immunology, Roswell Park Cancer Institute, Buffalo, NY, USA. Cancer Immunology Immunotherapy (1998), 46(1), 21-24. Publisher: Springer-Verlag, CODEN: CIIMDN ISSN: 0340-7004. Journal written in English. CAN 128:312832 AN 1998:233232 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A novel biodegradable poly(lactic acid) microsphere formulation was evaluated for in vivo cytokine immunotherapy of cancer in a human tumor xenograft/severe combined immunodeficiency (SCID) mouse model. Co-injection of interleukin-2 (IL-2)-loaded microspheres with tumor cells into a s.c. site resulted in the complete suppression of tumor engraftment in 80% of animals. In contrast, bovine serum albumin (BSA)-loaded particles or bolus injections of poly(ethylene glycol)/IL-2 were ineffective in preventing tumor growth. The antitumor effect of IL-2 released by the microspheres was shown to be mediated by the mouse natural killer cells. This is the first evidence that the rejection of human tumor xenografts can be provoked by the sustained in vivo delivery of IL-2 from biodegradable microspheres. The use of poly(lactic acid) microspheres to deliver cytokines to the tumor environment could provide a safer and simpler alternative to gene therapy protocols in the treatment of cancer.

Answer 25:

Bibliographic Information

Biodistribution of iodine-125 labeled monoclonal antibody/interleukin-2 immunoconjugate in athymic mice bearing human tumor xenografts. Nakamura, Kayoko; Kubo, Atsushi. Department of Radiology, Keio University School of Medicine, Tokyo, Japan. Cancer (New York) (1997), 80(12, Suppl.), 2650-2655. Publisher: John Wiley & Sons, Inc., CODEN: CANCAR ISSN: 0008-543X. Journal written in English. CAN 128:125387 AN 1998:12687 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Some vasoactive drugs have been studied in the hope of altering the vascular permeability and/or blood of tumors to enhance monoclonal antibody (MoAb) uptake. The pretreatment of interleukin-2 (IL-2), one of the vasoactive reagents, produced a generalized vascular permeability, but its function was not tumor specific. Conversely, MoAb/IL-2 immunoconjugates were developed that selectively alter the vasopermeability of tumors. In the current study the authors evaluated whether radiolabeled anti-carcinoembryonic antigen (CEA) MoAb, ZCE025/IL-2 immunoconjugate, specifically can enhance delivery of iodine-125 (I-125) to tumor sites. ZCE025 was conjugated with IL-2, and the conjugate then labeled with I-125. Biodistribution studies were performed in athymic mice bearing CEA-producing human tumor (MKN45) xenografts. Mice were injected with I-125-ZCE025/IL-2 conjugate, and I-125 activities in the organs, including blood and tumor, were investigated at 1, 3, and 5 days after injection. Vascular permeability of the organs, including tumors, also was studied by using I-131 labeled mouse serum albumin in three groups. I-125 labeled ZCE025/IL-2 conjugate destroyed its lymphokine-activated killer cell (LAK) activation, but retained a min. of 75% of the antibody binding reactivity. Biodistribution of I-125-ZCE025/IL-2 conjugate showed increased uptake of I-125 in tumor by a factor of 1.5, 4.2, and 4.1 compared with I-125-ZCE025 on Days 1, 3, and 5, resp. In contrast, I-125 distribution was not enhanced in any organs except the tumor. Vascular permeability studies demonstrated that the physiol. effect of IL-2 was tumor specific in the mice that received the I-125-ZCE025/IL-2 conjugate. These studies indicate that the administration of radiolabeled MoAb/IL-2 double conjugate may enhance the therapeutic potential of radiolabeled MoAb without any pretreatment with IL-2 or repeated injection of MoAb.

Answer 26:

Bibliographic Information

Superiority of sirolimus (rapamycin) over cyclosporine in augmenting allograft and xenograft survival in mice treated with antilymphocyte serum and donor-specific bone marrow. Hale, Douglas A.; Gottschalk, Rita; Fukuzaki, Takayuki; Wood, Mary L.; Maki, Takashi; Monaco, Anthony P. Division of Organ Transplantation, Department of Surgery, Deaconess Hospital and Harvard Medical School, Boston, MA, USA. Transplantation (1997), 63(3), 359-364. Publisher: Williams & Wilkins, CODEN: TRPLAU ISSN: 0041-1337. Journal written in English. CAN 126:233291 AN 1997:189164 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Sirolimus is a potent immunosuppressive agent with great therapeutic potential. The objective of our study was to evaluate the

efficacy of sirolimus vs. cyclosporine in augmenting the un-responsiveness induced by an antilymphocyte serum (ALS)/donor-specific bone marrow (BM)-based regimen across three levels of histoincompatibility: class I and II disparate (DBA/2 to B6AF1), complete mismatch (AKR to C57BL/6), and xenograft (ACI rat to B6AF1). Full-thickness skin grafts were taken from donors and placed on recipients in std. fashion. Seven groups of recipient mice (-28) received various combinations of the following treatment protocols: sirolimus, 1.5 mg/kg (3.0 mg/kg for xenografts) every other day from day 0 to day 12; cyclosporine, 50 mg/kg every other day from day 10 through 22; ALS, 0.5 mL on days -1 and 2 for allografts and days -1, 2, and 4 for xenografts; and BM, 25 million donor-specific cells IV on day 7. The administration of ALS or ALS/BM resulted in modest but significant prolongation of skin graft survival in all combinations tested. Cyclosporine combined with ALS or ALS/BM significantly extended allograft survival compared with ALS or ALS/BM alone but had no effect on xenograft survival. In contrast, the combination of sirolimus with ALS or ALS/BM resulted in a two- to threefold increase in allograft survival and over a fourfold increase in xenograft survival when compared with the comparable cyclosporine-based regimen. Addnl., lymphocytes isolated from class I and II incompatible mice with skin grafts surviving >100 days demonstrated markedly reduced interleukin 2 and interferon-γ secretion in response to irradiated donor-specific lymphocytes in culture. In the regimens tested, sirolimus was superior to cyclosporine in augmenting donor BM-induced skin graft prolongation in ALS-treated mice across all levels of histoincompatibility.

Answer 27:

Bibliographic Information

In vivo cytokine gene therapy of human tumor xenografts in SCID mice by liposome-mediated DNA delivery. Egilmez, N. K.; Cuenca, R.; Yokota, S. J.; Sorgi, F.; Bankert, R. B. Dep. Molecular Immunology, Roswell Park Cancer Inst., Buffalo, NY, USA. Gene Therapy (1996), 3(7), 607-614. Publisher: Stockton, CODEN: GETHEC ISSN: 0969-7128. Journal written in English. CAN 125:131887 AN 1996:437426 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The human interleukin-1 (IL-2) gene was successfully delivered into established human tumor xenografts in SCID (severe combined immunodeficient) mice by cationic liposome-mediated DNA delivery. A bicistronic mammalian expression vector contg. a reporter gene (β-galactosidase) and human IL-2 cDNA was complexed with either lipofectin of DC-cholesterol liposomes and transferred to tumor xenografts by direct intratumoral injection. Transfection of tumors was confirmed by staining of tumor sections for β-galactosidase activity and by reverse transcription-polymerase chain reaction (RT-PCR) for the presence of IL-2 mRNA. Growth suppression of tumor xenografts was obsd. in animals injected with plasmid-liposome complexes but not in animals that received liposomes or naked plasmid only. Complete tumor regression, mediated by the mouse natural killer cells was obsd. in 50-80% of the mice treated with the plasmid contg. the IL-2 cDNA. The effectiveness of the treatment was dependent on the transfection efficiency and the tumor size at the start of therapy. An initial IL-2 independent suppression of tumor growth was also obsd. with a plasmid carrying only the β-galactosidase gene but this effect was temporary and did not lead to tumor regression. These results establish that human tumor xenografts growing in SCID mice can be transfected in vivo by liposome mediated gene delivery r and that both IL-2-dependent and IL-2 Independent factors may contribute to the tumor suppression obsd. here.

Answer 28:

Bibliographic Information

Biodistribution of 18F- and 125I-labeled anti-Tac disulfide-stabilized Fv fragments in nude mice with interleukin 2.alpha. receptor-positive tumor xenografts. Choi, C. W.; Lang, L.; Lee, J. T.; Webber, K. O.; Yoo, T. M.; Chang, H. K.; Le, N.; Jagoda, E.; Paik, C. H.; et al. Dep. Nucl. Med., Natl. Inst. Health, Bethesda, MD, USA. Cancer Research (1995), 55(22), 5323-9. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 123:333821 AN 1995:942906 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We evaluated the biodistribution, pharmacokinetics, and generation of catabolites of an 18F- and 125I-labeled anti-Tac

disulfide-stabilized Fv fragment (dsFv) in tumor-bearing nude mice. This dsFv is genetically engineered from a murine monoclonal antibody that recognizes the alpha subunit of the interleukin 2 (IL-2.alpha.) receptor. Labeling was performed with 18F using N-succinimidyl 4-([18F]fluoromethyl)benzoate or with 125I using the Iodo-Gen method. The immunoreactivities of the radiolabeled anti-Tac dsFv were >82%. The biodistribution was evaluated (at 15, 45, and 90 min and 6 h) in athymic nude mice (.apprx.five/group) bearing s.c. tumor xenografts. Cell line A431 served as the IL-2 receptor-neg. control tumor, whereas the ATAC4 cell line served as our IL-2 receptor-pos. tumor. Animals received injections of 18F-labeled anti-Tac dsFv (0.1-0.4 megabecquerels/0.9-1 μg). Blood clearance for both prepns. was rapid, with <10% retained in the blood by 15 min. Max. accumulation in ATAC4 tumors occurred between 45 and 90 min and peaked at a mean of 4.2% injected dose/g (18F) and 5.6% of injected dose/g (125I). At 6 h, the ATAC4 tumors contained 11 times more 18F and 3 times more 125I than did the A431 tumors. The ATAC4 tumor:blood ratios for the 18F and 125I were >12:1 and >1.4:1 at 6 h, resp., whereas the ratios for the antigen-neg. A431 tumor were less than 1. The kidneys were the major route of elimination. Catabolites appeared quickly and were identified as [125I]iodide and predominantly N-ε-[18F]4-fluoromethylbenzoyl(α-N-acetyl) lysine. This is the first study to evaluate the biodistribution of an 18F-labeled fV fragment in vitro and in vivo. In vivo, the dsFv was taken up rapidly by the kidneys, producing lysine-contg. catabolites for 18F-labeled dsFv and [125I]iodide for 125I-labeled dsFv.

Answer 29:

Bibliographic Information

Eradication of large human B cell tumors in nude mice with unconjugated CD20 monoclonal antibodies and interleukin 2. Hoojberg, Erik; Sein, Johan J.; van den Berk, Paul C. M.; Hart, Augustinus A. M.; van der Valk, Martin A.; Kast, W. Martin; Melief, Cornelis J. M.; Hekman, Annemarie. Dep. Immunology, Netherlands Cancer Inst., Amsterdam, Neth. Cancer Research (1995), 55(12), 2627-34. Publisher: American Association for Cancer Research, CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 123:31187 AN 1995:631848 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Since antibody-dependent cellular cytotoxicity is considered an important mechanism by which mAbs may exert their antitumor effects, it seems likely that these antitumor effects can be enhanced by the activation of the appropriate effector cell populations. The authors used nude mice xenografted with human Daudi tumor cells as a model to compare the antilymphoma effects of unconjugated CD19 (CLB-CD19) and CD20 (BCA-B20) mAbs (IgG2a subclass) alone or in combination with recombinant human interleukin 2 (rhIL-2) or recombinant mouse granulocyte-macrophage colony-stimulating factor (rmGM-CSF). Treatment of established tumors with BCA-B20 or rhIL-2 or rmGM-CSF as a single agent, all resulted in highly significant decreases of tumor growth rates, but did not increase the no. of complete regressions. The combination of CLB-CD19 or BCA-B20 mAbs with rhIL-2 or rmGM-CSF resulted in larger decreases of growth rates than either of the agents alone. Complete eradication of large Daudi tumors could be achieved when treatment with BCA-B20 mAbs was combined with rhIL-2, but not with the combination of CLB-CD19 mAbs and rhIL-2 nor with the combination of BCA-B20 mAbs and rmGM-CSF. Cured animals kept for 2-3 mo after complete regression of the tumors were still tumor free. Regression of tumors was correlated with the infiltration of lymphocytes as well as macrophages into the tumor. This is the first report to show that unconjugated CD20 mAbs are to be preferred over unconjugated CD19 mAbs, and interleukin 2 over GM-CSF in the combinational treatment of large B cell tumors.

Answer 30:

Bibliographic Information

Human recombinant IL-2 augments immunoglobulin and induces rheumatoid factor production by rheumatoid arthritis lymphocytes engrafted into severe combined immunodeficient mice. Kaul, Rashmi; Sharma, Arun; Lisse, Jeffrey R.; Christadoss, Premkumar. Department of Microbiology and Immunology, University of Texas, Galveston, TX, USA. Clinical Immunology and Immunopathology (1995), 74(3), 271-82. CODEN: CLIIAT ISSN: 0090-1229. Journal written in English. CAN 122:211925 AN 1995:453308 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Recombinant (r) human IL-2 was administered in vivo to improve homing and engraftment of rheumatoid arthritis (RA) patients' peripheral blood mononuclear cells (PBMC) into severe combined immunodeficient (SCID) mice. Human rIL-2 treatment resulted in augmented human Ig prodn. and induced IgM rheumatoid factor (RF) of human origin in SCID-RA chimeras. The increment of human serum IgG in SCID-RA chimeras after IL-2 treatment ranged between 15 and 43% and for IgM between 50 and 98% during 2-8 wk postengraftment. Human IgM-RF was detectable after 1 to 2 wk after engraftment and persisted over a period of 10-13 wk. No RF was produced in SCID mice engrafted with PBMC from healthy individuals with or without exogenous rIL-2 administration. Thus, human rIL-2 expanded autoreactive clones involved in the prodn. of RF in the SCID-RA chimeras. The present study provides a novel approach to establish an in vivo SCID-RA model to study the cellular and mol. mechanisms involved in the prodn. of RF and development of a RA-like lesion.

Answer 31:

Bibliographic Information

Expression of interleukin 2 receptors on human carcinoma cell lines and tumor growth inhibition by interleukin 2. Yasumura, Satoshi; Lin, Wen-chang; Weidmann, Eckhart; Hebda, Patricia; Whiteside, Theresa L. Departments Pathology, University Pittsburgh School Medicine, Pittsburgh, PA, USA. International Journal of Cancer (1994), 59(2), 225-34. CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 121:298861 AN 1994:698861 CAPLUS

Abstract

We have previously shown that human squamous cell carcinomas (SCC) express the interleukin 2 receptor (IL2R)-α and -β chains, and that the ligand, IL2, directly inhibits growth of the tumor in vitro and in vivo in the tumor xenograft-nude mice model. We now show that the α and β chains of IL2R are expressed on a variety of human carcinoma cell lines and on normal human keratinocytes in early-stage cultures. While all carcinoma cells in a population expressed IL2R-α and -β proteins, in keratinocytes obtained from different normal donors, variable proportions of cells were pos., as measured by flow cytometry. The carcinoma lines and 2/5 keratinocyte lines studied were also found to contain transcripts for the IL2R-γ chain detectable by combined reverse transcription-PCR (RT-PCR) and hybridization with the specific cDNA probe. Incubation of the gastric (HR) or renal cell carcinoma (RCC) cell lines, but not of other IL2R+ carcinoma cell lines or normal keratinocytes, in the presence of IL2 resulted in dose-dependent inhibition of tumor cell growth. Monoclonal antibodies (MAbs) specific for IL2R-β chain completely reversed this growth inhibitory effect of IL2. The ligand, IL2, also down-regulated surface expression of its own receptor and of intercellular adhesion mol.-I (ICAM-1) or class 1 major histocompatibility complex (MHC) antigens on IL2R+ tumor cells. All carcinoma cells studied incubated in the presence of IL2 exhibited significantly increased sensitivity to growth-inhibitory effects of other cytokines such as interferon (IFN)-γ, tumor necrosis factor (TNF)-α or transforming growth factor (TGF)-β. IL2 inhibited growth of the HR cells by arresting a significant proportion of tumor cells in the G0/G1 phase of the cell cycle. Thus, IL2 can have direct effects on IL2R+ carcinoma cells, leading to changes in growth or to increases in sensitivity of tumor cells to cytostatic activities of other cytokines.

Answer 32:

Bibliographic Information

Effect of interleukin-2 on the biodistribution of technetium-99m-labeled anti-CEA monoclonal antibody in mice bearing human tumor xenografts. Nakamura, Kayoko; Kubo, Atsushi. School Medicine, Keio University, Shinjuku, Japan. European Journal of Nuclear Medicine (1994), 21(9), 924-9. CODEN: EJNMD9 ISSN: 0340-6997. Journal written in English. CAN 121:296163 AN 1994:696163 CAPLUS

Abstract

We have evaluated whether interleukin-2 (IL-2) at low doses can enhance delivery of radionuclides to tumor sites by improving the access of the radiolabeled antibody. The effects of 1000 or 2000 units of IL-2 on the biodistribution of technetium-99m-labeled anticarcinoembryonic antigen (CEA) monoclonal antibody, ZCE025, in athymic mice bearing human CEA-pos. tumor (MKN45)

xenografts were investigated. Treatment with IL-2 resulted in a significantly higher tumor uptake (1.2-1.5-fold) compared with the control group. Some normal organs, such as heart, lung, liver, spleen and kidneys, showed increased 99mTc uptake following the IL-2 treatment. Pretreatment with IL-2 also induced an enhancement of the permeability index for mouse IgG in tumors and in normal organs, whereas the blood flow in both normal organs and tumors remained at control levels. The effects of IL-2 were found to be dose-dependent. The IL-2 treatment increased the plasma CEA levels but not the CEA content in tumor tissues, suggesting that IL-2 enhanced the leakage of CEA from tumor to blood. The enhancement ratios of the tumor 99mTc-ZCE025 uptake following treatment with IL-2 were 1.4 and 1.8 in mice bearing small and large tumors, resp. Our exptl. results indicated that the low dose of IL-2 enhanced the vascular permeability sufficiently to increase the amt. of antibody delivered to the tumor target. Administration of IL-2 would render radioimmunotherapy more effective, esp. in patients with large tumor burdens.

Answer 33:

Bibliographic Information

Analysis of mouse xenogeneic T-cell responses and the effect of FK 506 on these responses and on skin xenograft rejection. Fukuzawa, M.; Okada, A. Med. Sch., Osaka Univ., Osaka, Japan. Transplantation Proceedings (1994), 26(2), 972-4. CODEN: TRPPA8 ISSN: 0041-1345. Journal written in English. CAN 121:221327 AN 1994:621327 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

In vitro studies were conducted to investigate: (1) the cellular requirement for primary and sec. cytotoxic T-lymphocyte responses and interleukin-2 prodn. by mouse spleen cells stimulated by closely related rat xenoantigens; and (2) the in vivo effect of FK 506 on antixenogenic T-cell responses and skin xenograft rejection. In order to prevent xenograft rejection, it is essential to suppress all T-cell functions and/or antibody prodn.

Answer 34:

Bibliographic Information

Constitutive secretion of soluble interleukin-2 receptor by human T cell lymphoma xenografted into SCID mice:. correlation of tumor volume with concentration of tumor-derived soluble interleukin-2 receptor in body fluids of the host mice. Wasik, Mariusz A.; Sioutos, Nicholas; Tuttle, Melissa; Butmarc, Janet R.; Kaplan, William D.; Kadin, Marshall E. Dep. Pathol., Beth Israel Hosp., Boston, MA, USA. American Journal of Pathology (1994), 144(5), 1089-97. CODEN: AJPAA4 ISSN: 0002-9440. Journal written in English. CAN 121:155319 AN 1994:555319 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Increased serum concn. of sol. α-chain receptor for interleukin-2 (sIL-2R) has been noted in patients with a variety of inflammatory conditions and lymphoid malignancies including T cell leukemia and lymphoma. Elevated sIL-2R serum levels seen in lymphoid malignancies appear to correlate with the clin. stage of disease. However, because sIL-2R is produced by normal activated lymphocytes, it has been uncertain whether serum sIL-2R in such conditions is derived from tumor cells or normal immune cells responding to the tumor. To address this question, the authors used a model of human (CD30+) anaplastic, large T cell lymphoma transplanted into immunodeficient SCID mice. Reverse transcription polymerase chain reaction of tumor RNA showed that the tumor, designated mJB6, contains mRNA for α-chain of human IL-2R. Furthermore, 15 to 25% of tumor cells stained with anti-human IL-2R α-chain mAb. Solid phase ELISA anal. of serum samples from mice bearing mJB6 lymphoma showed high concns. of human sIL-2R. None of the control mice without lymphoma or with human nonlymphoid tumors (prostatic carcinoma, ovarian carcinoma, and glioblastoma multiforme) showed detectable human sIL-2R. The sIL-2R serum titers of mJB6-bearing mice correlated strongly with tumor vol. ($P < 0.0001$). Tumors as small as 0.4 to 0.8 mm3 could be detected by this method. The sensitivity of sIL-2R ELISA exceeded at least 150 times the sensitivity of conventional radioisotopic tumor detection. Total resection of mJB6 tumors resulted in complete clearance of sIL-2R from the murine serum within 48 h with a half-life of 6 h. Accordingly, partial resection led to a significant decrease in sIL-2R followed by gradual increase with tumor regrowth. SIL-2R was also detected in the urine of

mJB6-transplanted mice. As in serum, urine concns. of sIL-2R were proportional to tumor mass ($P < 0.02$). Based on these findings the authors postulate that malignant cells are a major source of serum sIL-2R in patients with lymphoid tumors.
In addn., the data further support monitoring sIL-2R concn. in body fluids as a sensitive method to detect change in tumor vol. in such patients.

Answer 35:

Bibliographic Information

Antitumor effects of a bispecific antibody targeting CA19-9 antigen and CD16. Garcia de Palazzo, Irma; Holmes, Michele; Gercel-Taylor, Cicek; Weiner, Louis M. Dep. Med. Oncol., Fox Chase Cancer Center, Philadelphia, PA, USA. Cancer Research (1992), 52(20), 5713-19. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 117:249723 AN 1992:649723 CAPLUS

Abstract

Bispecific murine monoclonal antibodies that target tumor and FcγRIII (CD16) can promote relevant tumor lysis by large granular lymphocytes. For these antibodies to be clin. useful, their properties should be maintained in vivo, where competing human Ig, shed target antigen, and shed CD16 may be encountered. At a min., bispecific antibody antitumor effects should be preserved in whole blood. Furthermore, potentiation of tumor lysis should be reflected by demonstrating the ability of bispecific antibody-retargeted effector cells to infiltrate and mediate lysis of organized tumor. If these characteristics are demonstrated, and there is evidence of in vivo efficacy of bispecific antibody-based therapy in a relevant animal model, further clin. development of such antibodies would be warranted. In this report the ability of CL158 bispecific antibody supernatants to mediate lysis of SW948 tumor growing in monolayer is shown to be preserved in the presence of interleukin 2-activated whole blood. When SW948 cells were grown in vitro as multicellular human tumor spheroids, incubation with interleukin 2-activated lymphocytes (LAK cells) and CL158 led to structural and widespread necrosis. This was dependent on CL158 and resistant to competition by pooled human Ig or interleukin 2-exposed whole blood. These effects were not promoted by the monospecific antibodies produced by the parent clones of CL158 and were not obsd. when the IgG2a variant of CA19-9 antibody, which mediates conventional antibody-dependent cellular cytotoxicity, was used instead of its bispecific deriv. To examine the efficacy of bispecific antibody-based treatments on in vivo tumor, scid mice bearing early s.c. SW948 xenografts were treated with interleukin 2 for 5 consecutive days, supplemented by 3 i.v. injections of 107 human LAK cells and various antibodies. Treatment of mice bearing SW948 tumors with LAK cells did not retard tumor growth, but when CL158 was added, delays in tumor growth were obsd.
Tumor growth delay required treatment with both LAK cells and the bispecific antibody. Treatment with the IgG2a variant of CA19-9 antibody, alone or with LAK cells, had no effects on tumor growth. It is clear that human LAK cell treatment of animals bearing early, established s.c. tumors is enhanced by the addn. of bispecific antibodies with relevant binding characteristics. When compared with the IgG2a isotype variant of CA19-9 monoclonal antibody, this bispecific antibody offers the advantages of preservation of activity in physiol. conditions, infiltration and disruption of organized tumor in vitro, and antitumor effects in a relevant xenograft model.

Answer 36:

Bibliographic Information

Chemo-adoptive immunotherapy of nude mice implanted with human colorectal carcinoma and melanoma cell lines. Gazit, Zulma; Weiss, David W.; Shouval, Daniel; Yechezkeli, Michal; Schirrmacher, Volker; Notter, Michael; Walter, Jurgen; Kedar, Eli. Hadassah Med. Sch., Hebrew Univ., Jerusalem, Israel. Cancer Immunology Immunotherapy (1992), 35(2), 135-44. CODEN: CIIMDN ISSN: 0340-7004. Journal written in English. CAN 117:189954 AN 1992:589954 CAPLUS

Abstract

The antitumor effects of chemotherapy, recombinant human interleukin-2 (IL-2), recombinant human interferon α A/D (IFNα),

allogeneic human lymphokine-activated killer (LAK) cells, and antitumor monoclonal antibody (mAb), administered alone and in various combinations, were tested in athymic nude mice carrying human tumor xenografts. Treatment began 6-18 days after i.v. or i.p. inoculation of colorectal carcinoma or melanoma cell lines, when macroscopic growths were evident. Chemotherapy consisted of 2 or 3 courses of 5-fluorouracil (5-FU) or dacarbazine. IL-2 and/or IFNα were administered 3-5 times weekly for 1-3 wk, usually starting 2-5 days after chemotherapy. Human LAK cells were infused once or twice weekly for 2 or 3 wk concurrently with IL-2. In some expts., murine anticolorectal carcinoma mAb (SF25) was administered. In both tumor systems, chemotherapy alone or immunotherapy alone (IL-2, IL-2 + LAK cells, IFNα, IL-2 + IFNα ± LAK cells) had little or no therapeutic effects. Additive effects were obtained by combining chemotherapy with IL-2 and LAK cells or with IL-2 and IFNα. In the majority of the expts., the most effective combination was chemotherapy + IL-2 + IFNα + LAK cells. Treatment with mAb was beneficial in the colorectal carcinoma system when combined with 5-FU + IL-2 or 5-FU + IL-2 + IFNα. Homing expts. with radiolabeled human and mouse LAK cells injected i.v. showed increased early accumulation in the liver and lungs, whereas freshly explanted mouse splenocytes localized mostly in the spleen and liver. The tissue distribution pattern of human LAK cells was similar in normal and tumor-bearing mice (with lung metastases). Thus, combination of chemotherapy with cytokines and LAK cells can be partially effective for advanced solid human tumors even in the absence of the host's T-cell immune response. Preliminary expts.
showed that tumor-specific, anti-melanoma T-cell clones were effective in local (s.c.) tumor growth inhibition (Winn assay) following coinjection with the autologous tumor cells.

Answer 37:

Bibliographic Information

Effects of recombinant human interleukin-2 and tumor necrosis factor-α with or without interferon-γ on human thyroid tissues from patients with Graves' disease and from normal subjects xenografted into nude mice. Kasuga, Yoshio; Matsubayashi, Sunao; Akasu, Fumito; Miller, Naomi; Jamieson, Christopher; Volpe, Robert. Dep. Med., Wellesley Hosp., Toronto, ON, Can. Journal of Clinical Endocrinology and Metabolism (1991), 72(6), 1296-301. CODEN: JCEMAZ ISSN: 0021-972X. Journal written in English. (Correction of: CAN 115:27439 AN 1991:427439) CAN 115:277736 AN 1991:677736 CAPLUS

Abstract

The effects were compared to interleukin-2 (IL-2) or tumor necrosis factor-α (TNFα) administration with or without interferon-γ (IFNγ) on Graves' and normal thyroid tissue xenografts in the nude mouse (in the absence of an intact immune system) in terms of possible functional, immunol., or histol. changes. The dosages of recombinant human IL-2, TNFα, and IFNγ given to each mouse were 250, 800, and 4000 U, resp.; they were injected i.p. daily for 6 consecutive weeks. The parameters measured included the free T4 index, thyroid autoantibodies, and mouse TSH during the course of the study. Thyroid epithelial cell (TEC) HLA-DR expression was measured in thyroid tissue before xenotransplantation and at death; in addn., light microscopic studies were carried out at those times. There were no differences in thyroid function between the results in unstimulated (control) animals and those obtained with cytokine administration in either group of tissues, with the exception of the group receiving TNFα together with IFNγ; in this latter group, the free T4 index declined 4-6wk after commencement of treatment in the animals with normal thyroid tissues xenografts. The redn. of thyroid function induced by the combination of IFNγ and TNFα obsd. in normal thyroid tissue may be due to inhibition of thyroperoxidase and thyrpglobulin gene transcription. However there was no such effect on the Graves' thyroid tissue xenografts, perhaps because of the down-regulation of this tissue in response to cytokines, after having been released from long term in vivo immune stimulation. On the other hand, TNFα plus IFNγ induced TEC HLA-DR expression on both types of thyroid xenografts at death, although IL-2 alone did not induce HLA-DR expression, and INFγ induced TEC significantly only on normal thyroid xenografts (but not on Graves' xenografts). In light microscopic examn., Graves' thyroid xenografts treated with IL-2alone or TNFα plus IFNγ appeared normal at death.

In addn., normal thyroid xenografts treated with the same cytokines did not show discernible differences compared to those at human surgery or when the xenografts were untreated at death. Thus, Graves' TEC did not differ from normal TEC in any fashion at the time of death, aside from a reduced responsiveness to the stimuli applied. These observations are again consistent with the previous proposition that Graves' TEC are not unique or abnormal, and may be mere passive captives to immunol. events in relation to the pathogenesis of autoimmune thyroid disease.

Answer 38:

Bibliographic Information

Effects of recombinant human interleukin-2 and tumor necrosis factor-α with or without interferon-γ on human thyroid tissues from patients with Graves' disease and from normal subjects xenografted into nude mice. Kasuga, Yoshio; Matsubayashi, Sunao; Akasu, Fumito; Miller, Naomi; Jamieson, Christopher; Volpe, Robert. Dep. Med., Wellesley Hosp., Toronto, ON, Can. Journal of Clinical Endocrinology and Metabolism (1991), 27(6), 1296-301. CODEN: JCEMAZ ISSN: 0021-972X. Journal written in English. CAN 115:27439 AN 1991:427439 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The effects were compared of interleukin-2 (IL-2) or tumor necrosis factor-α (TNFα) administration with or without interferon-γ (IFNγ) on Graves' and normal thyroid tissue xenografts in the nude mouse (in the absence of an intact immune system) in terms of possible functional, immunol., or histol. changes. The dosages of recombinant human IL-2, TNFα, and IFNγ given to each mouse were 250, 800, and 4000 U, resp.; they were injected i.p. daily for 6 consecutive weeks. The parameters measured included the free T4 index, thyroid autoantibodies, and mouse TSH during the course of the study. Thyroid epithelial cell (TEC) HLA-DR expression was measured in thyroid tissue before xenotransplantation and at death; in addn., light microscopic studies were carried out at those times. There were no differences in thyroid function between the results in unstimulated (control) animals and those obtained with cytokine administration in either group of tissues, with the exception of the group receiving TNFα together with IFNγ; in this latter group, the free T4 index declined 4-6 wk after commencement of treatment in the animals with normal thyroid tissue xenografts. The redn. of thyroid function induced by the combination of IFNγ and TNFα obsd. in normal thyroid tissue may be due to inhibition of thyroperoxidase and thyroglobulin gene transcription. However, there was no such effect on the Graves' thyroid tissue xenografts, perhaps because of down-regulation of this tissue in response to cytokines, after having been released from long term in vivo immune stimulation. On the other hand, TNFα plus IFNγ induced TEC HLA-DR expression on both types of thyroid xenografts at death, although IL-2 alone did not induce HLA-DR expression, and IFNγ induced TEC significantly only on normal thyroid xenografts (but not on Graves' xenografts). In light microscopic examn., Graves' thyroid xenografts treated with IL-2 alone or TNFα plus IFNγ appeared normal at death.

In addn., normal thyroid xenografts treated with the same cytokines did not show discernible differences compared to those at human surgery or when the xenografts were untreated at death. Thus, Graves' TEC did not differ from normal TEC in any fashion at the time of death, aside from a reduced responsiveness to the stimuli applied. These observations are again consistent with the previous proposition that Graves' TEC are not unique or abnormal, and may be mere passive captives to immunol. events in relation to the pathogenesis of autoimmune thyroid disease.

Answer 39:

Bibliographic Information

Potentiation by interleukin 2 of Burkitt's lymphoma therapy with anti-pan B (anti-CD19) monoclonal antibodies in a mouse xenotransplantation model. Vuist, W. M. J.; Van Buitenen, F.; De Rie, M. A.; Hekman, A.; Ruemke, P.; Melief, C. J. M. Div. Immunol., Netherlands Cancer Inst., Amsterdam, Neth. Cancer Research (1989), 49(14), 3783-8. CODEN: CNREA8 ISSN: 0008-5472. Journal written in English. CAN 111:76235 AN 1989:476235 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

To study the immunotherapeutic potential of monoclonal antibodies (mAbs) directed against the human pan-B-cell antigen CD19, a xenotransplantation model was developed in which the human Burkitt's cell line Daudi is s.c. transplanted into nude mice. IgG1, IgG2b, and IgG2a isotype variants of the anti-CD19 mAb(CLB-CD19) were tested for their capacity to inhibit the growth of 10 × 106 Daudi cells injected s.c. into nude mice. When mAb treatment was started 30 min after the injection of tumor cells, only the IgG2a isotype of CLB-CD19 had a marked antitumor effect in vivo. If treatment with IgG2a anti-CD19 mAb alone was delayed until Day 10 after tumor injection, no therapeutic effect was obsd. However, the combination of this delayed mAb treatment with recombinant interleukin 2 (rIL-2) inhibited the growth of Daudi cells in the nude mice, while treatment with rIL-2 alone was ineffective. In vitro expts. showed that peritoneal exudate cells were able to inhibit the proliferation of Daudi cells in the presence of the IgG2a isotype variant of CLB-CD19 mAb but not in the presence of the other CLB-CD19 mAb isotype variants. Fresh nude mouse spleen cells did not mediate antibody-dependent cellular cytotoxicity against CLB-CD19 mAb-sensitized Daudi cells, irresp. of the isotype used for sensitization. Preculture of these spleen cells with rIL-2 induced antibody-dependent cellular cytotoxicity against CD19+ target cells sensitized with

CLB-CD19 mAb of all isotypes. These results indicate that it is possible to enhance mAb-dependent effector systems in vivo with the lymphokine rIL-2.

Answer 40:

Bibliographic Information

Recombinant interleukin-2 inhibits growth of human tumor xenografts in congenitally athymic mice. Bubenik, J.; Kieler, J.; Tromholt, V.; Indrova, M.; Lotzova, E. Inst. Mol. Genet., Czech. Acad. Sci., Prague, Czech. Immunology Letters (1987), 14(4), 325-30. CODEN: IMLED6 ISSN: 0165-2478. Journal written in English. CAN 107:5498 AN 1987:405498 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Administration of human recombinant interleukin-2 (RIL-2) into congenitally athymic (nu/nu) mice carrying s.c. transplants of HeLa, HU 609T and T24B human carcinoma cells partially inhibited growth of the human tumor xenografts. In vitro activation of nu/nu spleen cells with human RIL-2 resulted in generation of killer cells showing similar levels of cytolysis as RIL-2-activated spleen cells from heterozygous (nu/+) mice. The RIL-2-activated (LAK) cells were cytotoxic for a variety of mouse and human tumors, reaching the peak of their cytotoxic activity after 3 days of cultivation in the RIL-2-contg. medium. The cytotoxic activity of activated nu/nu spleen cells was reduced by treatment with antibody against glycolipid asialo GM1, the differentiation antigen of natural killer (NK) cells. This finding suggests that in addn. to the conventional, asialo GM1- LAK cells, asialo GM1+ activated NK cells participated in the cytotoxicity displayed by the IL-2 activated nu/nu killer spleen cells.

Answer 41:

Bibliographic Information

The activity of inducible nitric oxide synthase in rejected skin xenografts is selectively inhibited by a factor produced by grafted cells. Holan Vladimir; Pindjakova Jana; Zajicova Alena; Krulova Magdalena; Zelezna Blanka; Matousek Petr; Svoboda Petr Institute of Molecular Genetics, Academy of Sciences, Prague, Czech Republic. holan@img.cas.cz Xenotransplantation (2005), 12(3), 227-34. Journal code: 9438793. ISSN:0908-665X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 15807773 AN 2005177438 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: Production of nitric oxide (NO) by graft infiltrating macrophages has been suggested as an important effector mechanism of allograft rejection. Expression of the gene for the inducible NO synthase (iNOS) and the production of NO in rejected graft has been demonstrated in various models of allotransplantation. However, whether NO plays a role in rejection of skin xenografts has not been documented. METHODS: Explants of rejected skin allografts or xenografts (rat to mouse) were cultivated in vitro and the production of NO, interleukin (IL)-2, IL-4, IL-10 and interferon-gamma (IFN-gamma) by graft infiltrating cells was determined by the Griess reaction or ELISA. Effects of supernatants from cultures of xenograft explants on the expression of gene for iNOS, accumulation of iNOS protein and NO production were determined by RT-PCR or Western blots. Molecular mass of the factor with the suppressive activity was characterized by filtration on chromatography Sephacryl S-200 Superfine column. In addition, the effects of 2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine (AMT), a selective iNOS inhibitor, on survival of skin xenografts were tested. RESULTS: While explants of rejected mouse skin allografts produced substantial amounts of NO, undetectable or only very low levels of NO were found in supernatants from cultured rat skin xenografts. Cocultivation of bacterial lipopolysaccharide (LPS)-stimulated mouse macrophages which produce high quantities of NO, with pieces of rejected xenografts, but not of syngeneic grafts, allografts or normal rat skin, completely inhibited production of NO. Production of IL-6 and IL-10 by LPS-stimulated macrophages was not inhibited under the same conditions. The inhibition of NO production was mediated by a factor which was produced by rejected rat xenograft and which was eluted from chromatography Sephacryl S-200 Superfine column in a fraction representing a molecular mass of 67 kDa

The factor did not inhibit the expression of the gene for iNOS, reduce the level of iNOS protein in stimulated macrophages, or function as a scavenger of NO. Rather, the factor inhibited the function of iNOS. The finding that NO does not play an important role during rejection of skin xenografts is supported by the observation that treatment of graft recipients with AMT, a specific iNOS inhibitor, did not enhance xenograft survival, while the same treatment resulted in prolongation of survival of skin allografts. CONCLUSION: The results thus demonstrate that a 67-kDa molecule produced by rejected rat skin xenografts selectively inhibits iNOS activity in graft infiltrating macrophages. We suggest that NO does not play a significant role in rejection of skin xenografts as it does in the case of allograft rejection.

Answer 42:

Bibliographic Information

Delayed type hypersensitivity-associated cytokines in islet xenotransplantation: limited efficacy of interleukin-2- and tumor necrosis factor-alpha-blockade in interferon-gamma receptor-deficient mice. Benda B; Lycke N; Holstad M; Korsgren O Department of Oncology, Radiology, and Clinical Immunology, Uppsala University, Sweden Xenotransplantation (2000), 7(3), 206-13. Journal code: 9438793. ISSN:0908-665X. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 11021666 AN 2000465742 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

To investigate the role of interferon (IFN)-gamma and tumor necrosis factor (TNF)-alpha and their potential to replace each other in the process of fetal porcine islet-like cell cluster (ICC) xenograft rejection, mice with a targeted disruption of the IFN-gamma receptor gene and wild-type controls were transplanted with fetal porcine ICCs under the kidney capsule and given post-transplant treatment with the TNF-alpha-inhibiting agent MDL 201,449A. Some of the MDL 201,449A-treated IFN-gamma receptor-deficient mice received additional treatment with cyclosporinee (CsA). Evaluation of the xenografts was performed 7 days after transplantation (all groups), and in IFN-gamma receptor-deficient mice treated with MDL 201 449 A, also 10 and 13 days after transplantation. On day 7 after transplantation, a few CD3+ cells were seen accumulated peripherally in the ICC xenograft. Moderate to abundant numbers of F4/80+ and Mac-1+ cells surrounded a few remaining ICCs present within the xenograft. Histochemical visualization of cyanide-resistant endogenous peroxidase activity for detection of eosinophils demonstrated only small numbers of eosinophils present within the xenograft by day 7 after transplantation. An increased amount of eosinophilic granulocytes was not found until day 10 after transplantation, i.e. at a time when ICC xenograft rejection has already been completed. However, two out of six IFN-gamma receptor-deficient mice given post-transplant treatment with CsA and MDL 201,449A exhibited intact ICC xenografts with ICCs arranged in chords and duct-like structures on day 7 after transplantation. Taken together, findings in this study indicate that, in the pig-to-mouse model, IFN-gamma, TNF-alpha, and interleukin-2 seem to be of importance to fetal porcine ICC xenograft rejection. Nevertheless, in a majority of animals, other cytokines eventually substitute for the lack of IFN-gamma, TNF-alpha and interleukin-2.

Answer 43:

Bibliographic Information

Expansion of intermediate T cell receptor cells expressing interleukin-2 receptor alpha- beta+, CD8alpha+ beta+, and lymphocyte function-associated antigen-1+ in the liver in association with intrahepatic islet xenograft rejection from rat to mouse: prevention of rejection with anti-interleukin-2 receptor beta monoclonal antibody treatment. Ohtsuka K; Yasunami Y; Ikehara Y; Nagai T; Kodama S; Maki T; Tomita A; Abo T; Ikeda S Department of Surgery I, Fukuoka University School of Medicine, Japan Transplantation (1997), 64(4), 633-9. Journal code: 0132144. ISSN:0041-1337. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 9293878 AN 97438103 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND: The precise mechanisms involved in islet xenograft rejection remain unknown. The purpose of the present study was to determine cellular mechanisms responsible for islet xenograft rejection in the liver to facilitate finding a procedure for prevention of immune rejection. METHODS: Hepatic mononuclear cells (MNC) as well as splenocytes, peripheral blood MNC, and thymocytes from streptozotocin-induced diabetic mice (BALB/c) rejecting the intrahepatic rat (Lewis) islet xenografts were isolated and examined by two-color FACS analysis. RESULTS: The characteristic finding of the hepatic MNC from the mice rejecting islet xenografts compared with mice receiving isografts was a significant increase in the yield as well as in the percentage of the cells expressing CD3+ interleukin-2 receptor (IL-2R) alpha- beta+, CD3+ CD8alpha+ beta+, and T cell receptor (TCR) alphabeta+ lymphocyte function-associated antigen-1+. The expression of CD3 and TCR alphabeta of these T cells was found to be of intermediate intensity (TCR(int) cells). The expansion of these TCR(int) cells occurred predominantly in the liver. There was no significant difference in the cells expressing CD3+ IL-2R alpha+, CD3+ CD4+, CD3+ TCRgammadelta+, CD3- IL-2Rbeta+ (natural killer cells), and B220+ (B cells). In vivo administration of anti-IL-2Rbeta monoclonal antibody directed to the expanded cells produced a prevention of rejection. CONCLUSIONS: These findings suggest that islet xenograft rejection in the liver from rat to mouse is an event for which the TCR(int) cells are responsible.

Answer 44:

Bibliographic Information

Clinical development of 2B1, a bispecific murine monoclonal antibody targeting c-erbB-2 and Fc gamma RIII. Weiner L M; Clark J I; Ring D B; Alpaugh R K Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA Journal of hematotherapy (1995), 4(5), 453-6. Journal code: 9306048. ISSN:1061-6128. (CLINICAL TRIAL); (CLINICAL TRIAL, PHASE I); Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T); (RESEARCH SUPPORT, U.S. GOV'T, P.H.S.) written in English. PubMed ID 8581384 AN 96129482 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Bispecific monoclonal antibodies (BsmAb) can be used to specifically target tumor cells for cytotoxicity mediated by defined effector cells. One such BsmAb, 2B1, targets the extracellular domains of both the c-erbB-2 protein product of the HER-2/neu oncogene and Fc gamma RIII (CD16), the Fc gamma receptor expressed by human natural killer cells, neutrophils, and differentiated mononuclear phagocytes. 2B1 promotes the conjugation of cells expressing these target antigens. It efficiently promotes the specific lysis of tumor cells expressing c-erbB-2 by human NK cells and macrophages over a broad concentration range. 2B1 selectively targets c-erbB-2-positive human tumor xenografts growing in immunodeficient SCID mice. Treatment of such mice with 2B1 plus interleukin 2 (IL-2) inhibits the growth of early, established human tumor xenografts overexpressing c-erbB-2. A phase I clinical trial of 2B1 has been initiated to determine the toxicity profile and maximum tolerated dose (MTD) of this BsmAb and to examine the biodistribution of the antibody and the biologic effects of treatment. Preliminary results of this trial indicate that the dose-limiting toxicity for patients with extensive prior bone marrow-toxic therapy is thrombocytopenia for as yet undetermined reasons. Toxicities of fevers, rigors, and associated constitutional symptoms are explained, in part, by treatment-induced systemic expression of cytokines, such as tumor necrosis factor-alpha. Circulating, functional BsmAb is easily detectible in treatment patients' sera and exhibits complex elimination patterns. HAMA and anti-idiotypic treatment-induced antibodies are induced by 2B1 treatment. Some preliminary indications of clinical activity have been observed. BsmAb therapy targeting tumor antigens and Fc gamma RIII has potent immunologic effects. Future studies will include the development of more relevant animal models for BsmAb therapy targeting human Fc gamma RIII.

The ongoing phase I trial will be completed to identify the MTD for patients without extensive prior bone marrow-toxic chemotherapy and radiation. A phase II clinical trial of 2B1 therapy in women with metastatic breast cancer is planned, as is a phase I trial incorporating treatment with both 2B1 and IL-2.

Answer 45:

Bibliographic Information

Morphological assessment of grafted rat and mouse cortical neurons: a light and electron microscopic study. Lubke J; Wood M J; Clarke D J Department of Human Anatomy, University of Oxford, England The Journal of comparative neurology (1994), 341(1), 78-94. Journal code: 0406041. ISSN:0021-9967. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 8006225 AN 94274938 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The morphology of cortical neurons grafted into (or near) the rat striatum was studied by means of intracellular Lucifer yellow injections in fixed slices. Rat donor syngeneic cortical tissue (from postnatal day 1 old rats; AO strain) as well as mouse donor xenogeneic cortical tissue (prenatal day 19; C3H/HE strain) were grafted as solid pieces into 8-12 week-old rats (AO strain). Recipients of mouse xenografts were immunosuppressed with a monoclonal antibody against the interleukin-2 receptor. After perfusion and sectioning of the graft-containing areas, individual slices were incubated in the DNA stain 4.6-diamidino-2-phenylindole (DAPI) to visualize the cell nuclei. Grafts could be easily identified by a surrounding rim of astrocytes which outline the border between grafted and host tissue. Grafted cortical neurons were intracellularly filled with Lucifer yellow, DAB-photoconverted, and further processed for light and electron microscopy. In general, no cortical lamination could be observed in the grafted rat and mouse cortical tissue, but neurons were loosely packed throughout the graft. Two major cell types could be identified in all grafts investigated so far. The majority resembled those described as spiny neurons (85%), which could be further classified into pyramid-like, spiny stellate-like or fusiform spiny neurons, with somata ranging between 15 and 25 microns in diameter. The remaining 15% resembled non-spiny neurons with either a multipolar basket-like or fusiform morphology. Dendrites of spiny and non-spiny neurons, which could extend to distances up to 400 microns, were never seen to cross the astrocytic border, but some main axon and axonal collaterals of spiny neurons were found to leave the graft. On the basis of light microscopic observations no difference was found between mouse and rat grafted cortical neurons.

The results of this study show that grafted cortical neurons retain some of the characteristic features of neurons in the intact adult cerebral cortex, although there appears to be a greater preponderance of spiny neurons in grafted tissue. This may reflect an immaturity of the grafted tissue or a response to the striatal environment.

Answer 46:

Bibliographic Information

Transfer of interleukin 2 receptor genes into squamous cell carcinoma. Modification of tumor cell growth. Lin W C; Yasumura S; Whiteside T L Department of Pathology, School of Medicine, University of Pittsburgh, Pa Archives of otolaryngology--head & neck surgery (1993), 119(11), 1229-35. Journal code: 8603209. ISSN:0886-4470. (COMPARATIVE STUDY); Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 8217083 AN 94030921 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

OBJECTIVE: Human squamous cell carcinomas of the head and neck (SCCHN) have been shown to express interleukin 2 receptor (IL-2R), and binding of the ligand, IL-2, to the receptor results in tumor growth inhibition in vitro or in vivo in an SCCHN xenograft model in nude mice. To optimize growth inhibitory effects of IL-2, expression of the alpha or gamma chains of IL-2R in SCCHN was experimentally modified by transfection of tumor cells with the respective IL-2R genes or the lacZ gene as control. DESIGN: Using plasmid vectors containing the IL-2R alpha chain gene under the control of a cytomegalovirus promoter or the IL-2R gamma chain gene under the control of a Rous sarcoma virus promoter, the IL-2R genes were transferred by lipofection into SCCHN cell lines. Stable transfectants were selected, cloned by limiting dilution, and clones were compared with the parental cell lines for their sensitivity to the growth-inhibitory effect of IL-2. RESULTS: Transfer of the IL-2R alpha chain gene into SCCHN cells resulted in significant upregulation of expression of the IL-2R alpha chain on tumor cell surface but not in increased tumor growth inhibition by IL-2. In contrast, SCCHN IL-2R gamma transfectants, which expressed IL-2R gamma chain transcripts as confirmed in RNase protection assays, were significantly inhibited in growth and were sensitive to lower concentrations of IL-2 than the parental cell lines. CONCLUSIONS: Genetic modification of IL-2R expression on IL-2R-positive tumor cells in culture significantly alters

their proliferative response to IL-2. These observations open a way for developing new strategies for therapy of SCCHN based on direct interactions of IL-2 with its receptor on tumor cells.

Answer 47:

Bibliographic Information

Age-related decrease in transplantability of human tumours in nu/nu mice. Bubenik J; Kieler J; Jandlova T; Simova J Institute of Molecular Genetics, Czechoslovak Academy of Sciences, Flemingovo Anticancer research (1992), 12(5), 1695-8. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 1444237 AN 93073665 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Experiments were designed to assess age-related changes in the transplantability of human tumours xenografted in congenitally athymic (nu/nu) mice. It has been found that the number of progressively growing human tumour xenografts decreased significantly with increasing age of BALB/c nu/nu recipients. These findings, taken together with a previously recognized increase in the frequency of endogenous interleukin 2 (IL-2)-producing cells with age of nu/nu mice, prompted us to investigate whether administration of exogenous IL-2 to young adult nu/nu mice could change the transplantability of human tumours in the mice. Peritumoral administration of exogenous interleukin 2 to 8-week-old nu/nu mice inhibited the growth of the human tumour xenografts. In vitro activation of nu/nu splenocytes with exogenous Il-2 resulted in the generation of killer cells which have been found to be cytolytic when allowed to react with human tumour targets in 51Cr cytotoxicity assay. In addition, it has been found that the percentage of IL-2-activated Thy 1.2+ and ASGM1+ cells substantially increased with increasing age of nu/nu spleen cell donors. These findings are compatible with the hypothesis that the observed age-related decrease in takes of human tumour xenografts might be determined by the increasing level of IL-2 production and subsequent maturation of IL-2-dependent effector cells.

Answer 48:

Bibliographic Information

Local adoptive immunotherapy of human head and neck cancer xenografts in nude mice with lymphokine-activated killer cells and interleukin 2. Sacchi M; Snyderman C H; Heo D S; Johnson J T; d'Amico F; Herberman R B; Whiteside T L Department of Otolaryngology, University of Pittsburgh School of Medicine, Pennsylvania 15261 Cancer research (1990), 50(10), 3113-8. Journal code: 2984705R. ISSN:0008-5472. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2334906 AN 90242289 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The efficacy of local adoptive immunotherapy with human lymphokine-activated killer cells and recombinant interleukin 2 (rIL-2) in growth inhibition of established squamous cell carcinoma of the head and neck (SCCHN) was evaluated in a nude mouse model. The model of xenografted SCCHN was established by s.c. injections of in vitro maintained tumor cells (2-10 x 10(6) cells/mouse) into the flank of splenectomized animals pretreated with cyclophosphamide (200 mg/kg). The SCCHN line used was tumorigenic in 95% of the appropriately conditioned nude mice. Inhibition of tumor growth by locally administered effector cells was the end point of the study, since the tumors did not metastasize within 6 weeks of tumor challenge. Either i.p. or local administration of rIL-2 alone (1000 units/day) to the tumor site daily for 2 weeks resulted in a significant inhibition of tumor growth. In the absence of detectable natural killer activity in these mice, a modest dose of rIL-2 had a direct antitumor effect on SCCHN cells in vivo. In addition, complete inhibition of tumor growth was achieved with 3 times weekly injections of 5-10 x 10(6) lymphokine-activated killer cells delivered to the tumor site and 1000 units of rIL-2 administered locally every day for 2 weeks. Our data indicate that local or systemic

immunotherapy with rIL-2 alone or local adoptive immunotherapy with an adequate dose of lymphokine-activated killer cells plus rIL-2 may be effective in preventing the growth of established SCCHN tumors in vivo.

Answer 49:

Bibliographic Information

Adoptive cellular immunotherapy to the endometrial carcinoma cell line xenografts in nude mice. Shimizu H; Inoue M; Tanizawa O Department of Obstetrics and Gynecology, Osaka University Medical School, Japan Gynecologic oncology (1989), 34(2), 195-9. Journal code: 0365304. ISSN:0090-8258. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 2787771 AN 89326310 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The present study was designed to examine the immunotherapeutic properties of lymphokine-activated killer (LAK) cells against uterine endometrial cancers. Three endometrial cancer cell lines, ISHIKAWA, SNG-M, and HHUA, were shown to be specifically lysed in short-term 51Cr-release assay, although the susceptibility was different among the cell lines. The xenograft tumors of ISHIKAWA and SNG-M exhibited high susceptibility to LAK cells in the in vitro assay and responded well to the adoptive transfer of LAK cells in nude mice. On the other hand, the xenograft of HHUA showed low reactivity to LAK cells and showed no response to the adoptive immunotherapy. However, the adoptive transfer of LAK cells combined with intraperitoneal administration of both recombinant interleukin-2 (rIL-2) and lentinan markedly inhibited the growth of HHUA xenografts in nude mice, while no response was observed in nude mice treated with LAK cells plus either rIL-2 or lentinan, or treated with rIL-2 plus lentinan alone. These results suggest the clinical application of adoptive immunotherapy in association with LAK cells, rIL-2, and lentinan as a treatment of gynecologic cancers.

Answer 50:

Bibliographic Information

Influence of interleukin II on xenotransplanted grade 3 to 4 glioma in nude mice. Weber F; List J; Rommel T; Menzel J; Symas J; Pohl U; Mohr H; Schmitz R; Amue B Department of Neurosurgery, University of Cologne Strahlentherapie und Onkologie : Organ der Deutschen Rontgengesellschaft ... [et al] (1989), 165(7), 556-8. Journal code: 8603469. ISSN:0179-7158. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 2546273 AN 89317866 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))